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RESEARCH ARTICLE

Exploring the Clinical Signs and Underlying Processes of Drug-Induced Nephrotoxicity: A concentrated review…

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ABSTRACT

Introduction: *Nephrotoxicity caused by medicine is a prevalent side effect of many drugs. It can occur as an inpatient or outpatient condition and range in severity from a minor, treatable injury to a severe kidney disease. Symptoms of drug-induced nephrotoxicity include proteinuria, acid-base abnormalities, abnormal urine tests, electrolyte imbalances, hematuria, pyuria, and, most frequently, a decrease in the glomerular filtration rate. Pharmaceuticals or pharmacologic classes have several causes of drug-induced nephrotoxicity, and these reasons are typically categorized based on the histology of the injured kidney. Examples of drug-induced nephrotoxicity include aminoglycoside drugs, radiocontrast material, amphotericin B, selective cyclooxygenase-2 inhibitors, angiotensin-converting enzyme inhibitors, and selective cyclooxygenase-2 inhibitors. This review explores both the clinical signs and underlying processes of drug-induced nephrotoxicity.*

Aim: *The present study concentrates on the reasons and mechanisms of the nephrotoxicity caused by medicines.*

Methods: *The Iraqi Virtual Scientific Library, Google Scholars, and PubMed are the main sources that were relied upon to complete this review.*

Results: *The review demonstrates that different kinds of renal disease can be caused by regular drug use via multiple pathways.*

Conclusion: *Investigation into the crucial problem of drug-induced nephrotoxicity is necessary in order to fully comprehend the mechanisms causing renal damage and how to avoid it. To avoid the negative effects of nephrotoxicity, it is advantageous to maintain proper and consistent hydration, replenish lost electrolytes, and refrain from taking concurrent medications.*

Keywords: Nephrotoxicity; Adverse effect; Drugs.

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INTRODUCTION

One frequent site of drug-induced toxicity is the kidney. Drug-induced nephrotoxicity still remains a significant issue in the medical setting, where the administration of nephrotoxic medications is frequently required. The outcome is usually acute renal damage, which is a topical issue that needs to be discussed (Wu & Huang, 2018). However, nephrotoxicity can be difficult to anticipate during preclinical drug development and is commonly detected after the drugs have been used clinically. In this section, we'll discuss the approaches that are currently used to create such models. There is an overview of recent developments in stem cell-based methods as well as three-dimensional and microfluidic models. Several in vitro models have poor predictability and have only been investigated with a few chemicals. Nonetheless, a lot of studies looked into more substances and established whether the pertinent in vitro model was predictable. The findings show that using primary or stem cell-derived human kidney cells in conjunction with the appropriate markers can produce highly predictable results (Soo et al., 2018). By identifying at-risk patients, assessing the patient's renal function using the glomerular filtration rate (GFR), and ensuring the right dosage, drug-induced nephrotoxicity can be minimized to the lowest possible level (Zhang et al., 2021).

A. Mechanisms of Drug-Induced Nephrotoxicity

Drug-induced nephrotoxicity refers to kidney damage caused by certain medications or drugs. The mechanisms of drug-induced nephrotoxicity can vary depending on the drug and the individual's susceptibility. Some of the common mechanisms include (Kwiatkowska et al., 2021):

1. Direct toxicity: Some drugs can directly damage the kidney cells, leading to nephrotoxicity. For example, aminoglycoside antibiotics such as gentamicin and amikacin can cause direct toxicity to the renal tubular cells.

2. Immune-mediated toxicity: Some drugs can trigger an immune response that leads to kidney damage. This is known as immune-mediated toxicity. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen can cause immune-mediated interstitial nephritis.

3. Oxidative stress: Some drugs can cause oxidative stress in the kidneys, leading to cell damage and inflammation. This mechanism is seen with drugs such as cisplatin, which is used in chemotherapy.

4. Alteration of renal blood flow: Some drugs can alter renal blood flow, leading to decreased oxygen supply to the kidneys and subsequent cell damage. This mechanism is seen with drugs such as angiotensin-converting enzyme (ACE) inhibitors used for hypertension.

5. Metabolic disturbances: Certain drugs can cause metabolic disturbances that lead to kidney damage. For example, methotrexate used in cancer treatment can cause hyperuricemia, which leads to crystal deposition in the kidneys and subsequent nephrotoxicity. In conclusion, drug-induced nephrotoxicity is a complex process that involves various mechanisms depending on the drug involved. Understanding these mechanisms is crucial for preventing and managing drug-induced kidney injury in patients receiving medication therapy.

B. Tubular Epithelial Cell Damage

a. Acute Tubular Necrosis

Acute tubular necrosis (ATN) is a type of kidney injury that occurs when there is damage to the tubular cells of the kidneys. This can be caused by a variety of factors, including drugs.

Drugs that can cause ATN include (Kwiatkowska et al., 2021; Morales-Alvarez, 2020):

1. Nonsteroidal anti-inflammatory drugs (NSAIDs): These are commonly used to treat pain and inflammation, but they can also cause kidney damage if taken in high doses or for long periods of time.

2. Aminoglycoside antibiotics: These are powerful antibiotics that are used to treat serious infections, but they can also cause kidney damage if given in high doses or for too long.

3. Contrast agents: These are dyes that are used during certain medical procedures, such as CT scans and angiograms. They can cause kidney damage in some people, particularly those with pre-existing kidney problems.

4. Chemotherapy drugs: Some chemotherapy drugs can cause ATN as a side effect.

5. Antiviral medications: Certain antiviral medications used to treat hepatitis C and HIV can cause ATN.

Symptoms of ATN caused by drugs may include decreased urine output, swelling in the legs and feet, nausea and vomiting, fatigue, confusion, and seizures in severe cases (Booth, 2023). Treatment may involve stopping the offending drug, supportive care such as dialysis or fluid management, and addressing any underlying conditions that may have contributed to the development of ATN (LaForge et al., 2023).

C. Tubulointerstitial Disease

a. Acute Allergic Interstitial Nephritis

Acute allergic interstitial nephritis (AIN) is a type of kidney disease that is caused by an allergic reaction to certain medications. AIN is characterized by inflammation of the interstitial tissue of the kidneys, which can lead to kidney dysfunction and failure if left untreated. The most common drugs that because AIN include antibiotics such as penicillin, cephalosporin, and sulfonamides, as well as nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen (Caravaca-Fontán et al., 2019). Other medications that have been associated with AIN include proton pump inhibitors, diuretics, and anticonvulsants. Symptoms of AIN may include fever, rash, joint pain, nausea, vomiting, and swelling in the legs or feet. However, some people with AIN may not experience any symptoms at all (Alotaibi et al., 2022). Diagnosis of AIN typically involves a combination of blood tests to assess kidney function and urine tests to look for signs of inflammation or infection. In some cases, a kidney biopsy may be necessary to confirm the diagnosis. Treatment for AIN involves discontinuing the medication that caused the reaction and providing supportive care to manage symptoms. In severe cases where kidney function is significantly impaired, dialysis may be necessary until the kidneys are able to recover. Prevention of AIN involves careful monitoring of medication use and avoiding medications known to cause this condition in individuals who have a history of drug allergies or kidney disease (Mody et al., 2020).

D. Glomerular Disease

Glomerular disease by drugs refers to the damage caused to the glomeruli, which are tiny blood vessels in the kidneys responsible for filtering waste products from the blood, due to the use of certain medications. This can lead to impaired kidney function and potentially serious complications. Some drugs that can cause glomerular disease include (Shields, 2021):

1. Nonsteroidal anti-inflammatory drugs (NSAIDs): These are commonly used painkillers such as ibuprofen and naproxen. Prolonged use of these drugs can cause acute interstitial nephritis, a type of glomerular disease that causes inflammation and damage to the kidney tubules.

2. Antibiotics: Certain antibiotics such as penicillin, cephalosporin, and sulfonamides can cause allergic reactions that lead to glomerulonephritis, a type of glomerular disease characterized by inflammation and damage to the glomeruli.

3. Chemotherapy drugs: Some chemotherapy drugs used in cancer treatment can cause nephrotic syndrome, a type of glomerular disease that causes excessive protein loss through urine due to damage to the glomeruli.

4. Immunosuppressant: Drugs used to suppress the immune system such as cyclosporine and tacrolimus can cause focal segmental glomerulosclerosis (FSGS), a type of glomerular disease that causes scarring and damage to some parts of the glomeruli.

5. Contrast agents: These are substances used in medical imaging tests such as CT scans and MRI scans. They can cause acute kidney injury or nephrotic syndrome if they accumulate in the kidneys and damage the glomeruli. Treatment for drug-induced glomerular disease depends on the underlying cause and severity of symptoms. In some cases, stopping or changing medications may be necessary while in others, supportive care such as dialysis or kidney transplant may be required. It is important to always consult a healthcare provider before starting or stopping any medications.

E. Renal Vasculitis and Thrombosis

Renal vasculitis is a condition in which the blood vessels in the kidneys become inflamed, leading to damage and dysfunction of the kidneys. Thrombosis, on the other hand, is the formation of blood clots within blood vessels, which can obstruct blood flow and cause tissue damage. Drug-induced renal vasculitis and thrombosis are rare but serious side effects of certain medications. Some drugs that have been associated with these conditions include (O'Callaghan, 2023):

1. Anticoagulants: These drugs are used to prevent blood clots from forming. However, they can also increase the risk of bleeding and thrombosis.

2. Chemotherapy drugs: Some chemotherapy drugs can cause inflammation of the blood vessels and increase the risk of thrombosis.

3. Antibiotics: Certain antibiotics, such as penicillin and sulfonamides, have been associated with renal vasculitis.

4. Nonsteroidal anti-inflammatory drugs (NSAIDs): These drugs can cause kidney damage and increase the risk of thrombosis.

5. Immunosuppressant: Drugs used to suppress the immune system, such as cyclophosphamide and azathioprine, can increase the risk of renal vasculitis and thrombosis. Symptoms of drug-induced renal vasculitis may include fever,

fatigue, joint pain, skin rash, abdominal pain, and kidney dysfunction. Symptoms of drug-induced thrombosis may include swelling or pain in the affected area, redness or discoloration of skin overlying affected veins or arteries (Sheerin & Ramachandran, 2023). Treatment for drug-induced renal vasculitis and thrombosis may involve discontinuing the offending medication and using other medications to manage symptoms or prevent further complications. In severe cases, hospitalization may be necessary for close monitoring and supportive care (Rosner et al., 2021).

F. Obstructive Nephropathy

a. Intratubular Obstruction

Intratubular obstruction by drugs refers to the blockage of the renal tubules by medications or other substances, leading to impaired kidney function. This can occur due to the accumulation of drugs or their metabolites in the tubules, causing damage and inflammation. Some common drugs that can cause intratubular obstruction include nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, chemotherapeutic agents, and antiviral medications (Boyer et al., 2023). Symptoms of intratubular obstruction may include decreased urine output, swelling in the legs and feet, fatigue, nausea, and vomiting. Treatment typically involves discontinuing the offending medication and providing supportive care to manage symptoms and prevent further kidney damage. In severe cases, dialysis may be necessary to remove excess fluids and waste products from the body (Tuan et al., 2022).

G. Hemodynamically-Mediated Kidney Injury

Hemodynamically-mediated kidney injury (HDKI) is a type of kidney injury that occurs due to changes in blood flow to the kidneys. This can be caused by various factors, including drugs. Some drugs can cause HDKI by affecting the blood vessels that supply the kidneys or by altering the balance of hormones and chemicals that regulate blood flow. Examples of drugs that can cause HDKI include (Para et al., 2019):

1. Nonsteroidal anti-inflammatory drugs (NSAIDs): These drugs are commonly used to treat pain and inflammation. However, they can also cause HDKI by reducing blood flow to the kidneys and increasing the risk of kidney damage.

2. Angiotensin-converting enzyme (ACE) inhibitors: These drugs are used to treat high blood pressure and heart failure. They work by dilating blood vessels, which can reduce blood flow to the kidneys and increase the risk of HDKI.

3. Diuretics: These drugs are used to treat conditions such as high blood pressure and edema by increasing urine output. However, they can also cause HDKI by reducing blood volume and altering electrolyte balance.

4. Contrast agents: These are substances used in medical imaging procedures such as CT scans and angiograms. They can cause HDKI by damaging the blood vessels in the kidneys or altering blood flow.

5. Chemotherapy drugs: Some chemotherapy drugs can cause HDKI by damaging the cells that line the blood vessels in the kidneys or altering blood flow. Preventing HDKI caused by drugs involves careful monitoring of patients who are at risk for kidney injury, adjusting drug dosages based on kidney function, and avoiding combinations of medications that increase the risk of HDKI. In some cases, alternative medications may be recommended to reduce the risk of kidney injury (Bishoff & Kavoussi, 2022).

H. Prevention strategies

1. Dose adjustment: The dose of the drug should be adjusted according to the patient's renal function. This can be done by monitoring serum creatinine levels and adjusting the dose accordingly (Verbeeck & Musuamba, 2009).

2. Avoid nephrotoxic drugs: If possible, avoid using drugs that are known to be nephrotoxic or have a high risk of causing kidney damage (Sales & Foresto, 2020).

3. Hydration: Adequate hydration is important in preventing drug-induced nephrotoxicity. It helps to flush out the drug and its metabolites from the kidneys (Dobrek, 2023).

4. Monitoring: Regular monitoring of renal function is important in patients who are taking nephrotoxic drugs. This can help detect early signs of kidney damage and prevent further damage (Boivin et al., 2023).

5. Use of alternative medications: In some cases, alternative medications may be available that are less likely to cause kidney damage (Lameire et al., 2021).

6. Avoiding drug interactions: Some drugs can interact with each other and increase the risk of kidney damage. It is important to avoid such interactions by carefully monitoring drug combinations (Santos-Díaz et al., 2020).

7. Patient education: Patients should be educated about the risks associated with certain medications and advised on how to take them safely, including proper dosing and hydration (Organization, 2019).

8. Avoiding prolonged use: Prolonged use of certain medications can increase the risk of kidney damage. It is important to limit the duration of treatment wherever possible (James et al., 2020).

9. Genetic testing: In some cases, genetic testing may be useful in identifying patients who are at increased risk of developing drug-induced nephrotoxicity due to genetic factors (Awdishu et al., 2020; Dobrek, 2023).

10. Renal protective agents: Some medications may help protect the kidneys from damage caused by other drugs or toxins, such as antioxidants or anti-inflammatory agents (Mombeini et al., 2022).

I. The appropriate drug dosing adapted to altered kinetics

Drug induced nephrotoxicity is a common problem that can occur due to altered pharmacokinetics in patients with renal impairment. To avoid this, appropriate drug dosing should be adapted to the altered kinetics of the patient. The following are some strategies that can be used to avoid drug induced nephrotoxicity (Vondracek et al., 2021):

1. Adjusting the dose: The dose of the drug should be adjusted based on the patient's renal function. This can be done by calculating the creatinine clearance or estimated glomerular filtration rate (eGFR) and adjusting the dose accordingly (Delanaye et al., 2022).

2. Monitoring drug levels: Some drugs have narrow therapeutic windows and require monitoring of drug levels to ensure that they are within a safe range. This is particularly important in patients with renal impairment as altered pharmacokinetics can affect drug levels (Laracuente et al., 2020).

3. Choosing alternative drugs: In some cases, it may be necessary to choose alternative drugs that are less likely to cause nephrotoxicity or have a lower risk of adverse effects in patients with renal impairment (Sales & Foresto, 2020).

4. Avoiding nephrotoxic drugs: Certain drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, and contrast agents are known to cause nephrotoxicity and should be avoided or used with caution in patients with renal impairment (LaForge et al., 2023).

5. Monitoring for adverse effects: Patients with renal impairment should be closely monitored for signs of adverse effects such as changes in urine output, electrolyte imbalances, and acute kidney injury. In conclusion, appropriate drug dosing adapted to altered kinetics is essential to avoid drug induced nephrotoxicity in patients with renal impairment. Healthcare providers should carefully consider each patient's individual needs and adjust treatment accordingly to ensure optimal outcomes (Park et al., 2019)..

METHOD

The Iraqi Virtual Scientific Library, Google Scholars, and PubMed are the main sources that were relied upon to complete this review.

RESULTS

The review demonstrates that different kinds of renal disease can be caused by regular drug use via multiple pathways.

CONCLUSIONS

Drugs induced nephrotoxicity is a serious condition that can lead to kidney damage and failure. The mechanisms of nephrotoxicity vary depending on the drug and can include direct toxicity, immune-mediated reactions, and metabolic disturbances. It is important for healthcare providers to be aware of the potential for drug-induced nephrotoxicity and to monitor patients closely for signs of kidney dysfunction. Prevention strategies such as dose adjustments, hydration, and avoiding concurrent use of nephrotoxic drugs can help reduce the risk of this complication. Early recognition and management of drug-induced nephrotoxicity are crucial in preventing irreversible kidney damage.

AUTHOR'S CONTRIBUTIONS

The completion of this review was a collaborative effort, with each author making valuable contributions to the research process. The primary sources relied upon to gather information and data for this review were the Iraqi Virtual Scientific Library, Google Scholars, and PubMed.

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